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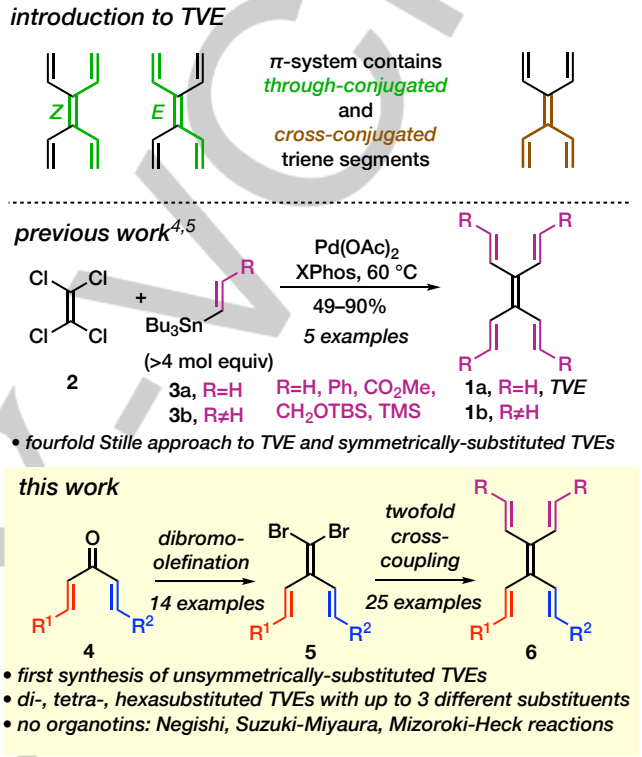
A Broad-Spectrum Synthesis of Tetravinylethylenes

Kelsey L. Horvath,[a] Christopher G. Newton,[a] Kimberley A. Roper,[a] Jas S. Ward[a] and Michael S. Sherburn*[a]

Abstract: The first general synthesis of compounds of the tetravinylethylene (TVE) family is reported. Ramirez-type dibromo-olefination of readily accessible penta-1,4-dien-3-ones generates 3,3-dibromo[3]dendralenes, which undergo twofold Negishi, Suzuki-Miyaura or Mizoroki-Heck reactions with a wide variety of olefinic coupling partners. This route delivers a broad range of unsymmetrically–substituted tetravinylethylenes with up to three different alkenyl substituents attached to the central C=C bond. The extensive scope of the approach is demonstrated by the preparation of the first higher order oligo-alkenic through-conjugated/cross-conjugated hybrid compounds. An unsymmetrically-substituted TVE is shown to undergo a domino electrocyclization-cycloaddition with high site-selectivity and diastereoselectivity, thereby demonstrating the substantial synthetic potential of substituted TVEs for controlled, rapid structural complexity generation.

Tetravinylethylene (TVE) is one of the smallest structures exhibiting both through-conjugation and cross-conjugation (Scheme 1). Specifically, the structure comprises intersecting pairs of *(E)*-1,3,5-hexatrienes, *(Z)*-1,3,5-hexatrienes and 2-methylene-1,4-pentadienes ([3]dendralenes). Nothing is known about the impact of substitution upon the behavior of TVEs and how this might be exploited. Furthermore, related structures containing more than five C=C units have not been reported in the literature. The first synthesis of TVE, a landmark contribution from the classical era of unsaturated hydrocarbon chemistry, was reported by Skattebøl and co-workers in the 1960s.[1-3] We recently disclosed the first preparatively useful approach to TVE, a one-step multi-gram scale synthesis, and demonstrated that the hydrocarbon is bench-stable when stored as a neat liquid.[4,5] The one-step synthesis of TVE (Scheme 1, **1a**) utilized a Pd(0)-catalyzed fourfold Stille cross-coupling sequence between tetrachloro-ethylene **2** and vinyltributylstannane **3a**. In addition to the parent TVE, five symmetrically-substituted TVEs **1b** were similarly prepared using substituted alkenyltributylstannanes **3b** in the exhaustive Stille cross-coupling process.[4,5]

As a starting point for future synthetic applications, the parent TVE has been shown to rapidly generate multi-cyclic systems.[4,5] Additionally, the hybrid through/cross-conjugated structure of the TVE unit represents the smallest organic four-directional branch point in a possible conducting molecular wire.[6] To realize the potential of the TVE family in target synthesis and materials applications, synthetic access to unsymmetrically-substituted systems must be granted. Until now, no unsymmetrically-substituted TVEs have been reported. Our previous synthetic approach (Scheme 1), in common with all other substituted TVE syntheses reported in the literature,[7] is only suited to the attachment of four identical substituted alkenyl-groups to the central C=C core.



Scheme 1. The existing synthetic route to TVEs with its limitations, and the new, broad scope synthesis.

Herein we report a broad-reaching solution, delivering the first 29 unsymmetrically substituted TVEs carrying up to three different substituents (Scheme 1, bottom). We also report the first compounds exhibiting extended π-systems based upon TVE subunits. Moreover, we establish the synthetic potential of these unsymmetrically-substituted TVEs, by way of a one-pot, site-selective and diastereoselective domino pericyclic sequence that generates three C–C bonds and six contiguous stereocenters. The new synthetic approach (Scheme 1, bottom) involves the conversion of penta-1,4-dien-3-ones **4** (readily accessed through twofold aldol-type condensations) into 3,3-dibromo-[3]dendralenes **5**, which in turn undergo a range of twofold cross-couplings to furnish diversely-substituted tetravinyl-ethylenes **6**.

Twelve substituted penta-1,4-dien-3-ones **4** were prepared, by way of sequential Claisen-Schmidt condensations[8] (see SI for details). There are only three examples of Ramirez dibromo-olefinations of penta-1,4-dien-3-ones **4** in the literature[9-11] and, in our hands, low yields were obtained under standard Ramirez reaction conditions.[12] Gratifyingly, in the majority of cases, the modified protocol introduced by Lautens and co-workers[13]

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furnished workable yields, and twelve substituted 3,3-dibromo[3]dendralenes[14] **5** were prepared in this manner (Table 1).

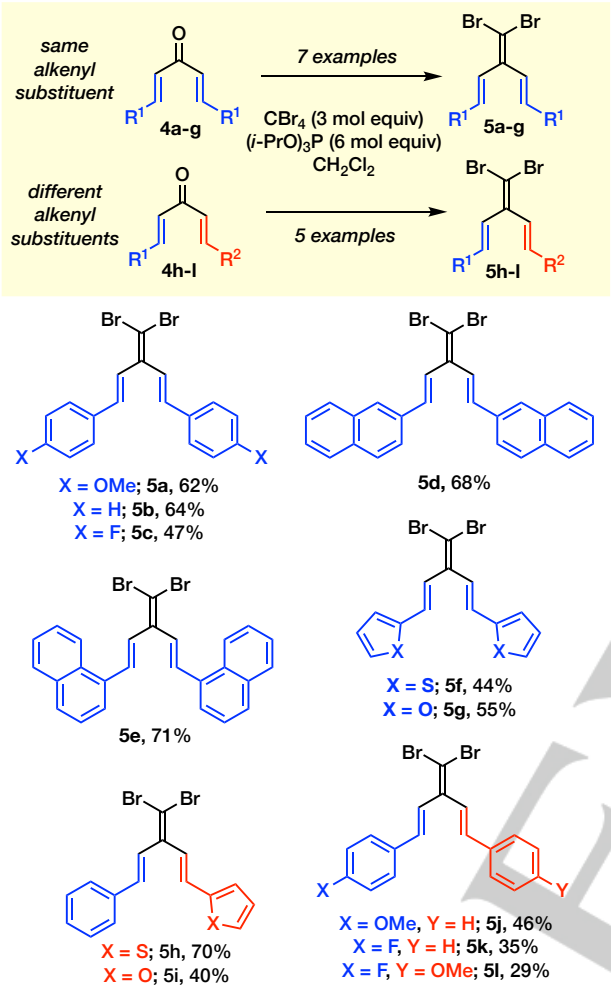


Table 1. Lautens-modified Ramirez dibromo-olefination of penta-1,4-dien-3-ones **4** permits the first general synthesis of 3,3-dibromo[3]dendralenes **5**.

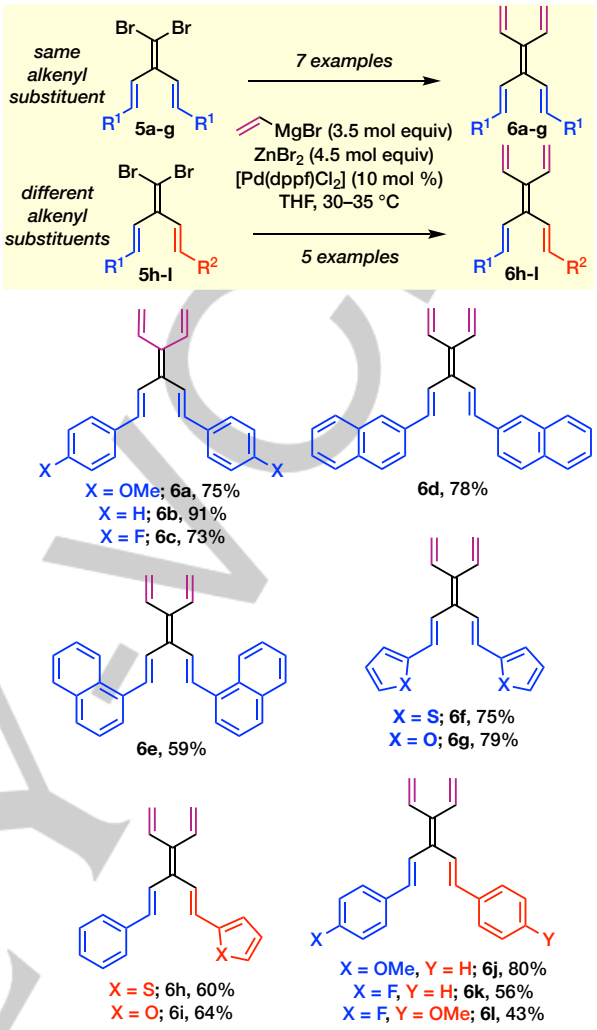


Table 2. Twofold Negishi cross-coupling of 3,3-dibromo[3]dendralenes **5** with vinylzinc bromide furnishes the first unsymmetrical tetravinylethylenes **6**.

Unlike some other dendralenic structures, which exhibit a propensity to dimerize and polymerize,[15] 3,3-dibromo[3]dendralenes **5** are generally white or yellow crystalline solids that can be stored neat without appreciable decomposition, and are easily handled using standard laboratory techniques.

While there are many examples of cross-coupling reactions of 1,1-dibromoalkenes in the literature,[16] there is only one example of a cross-coupling of a 3,3-dibromo[3]dendralene, involving the Sonogashira sp^2–sp coupling of a cyclic system with trimethylsilylacetylene.[10] In light of the lack of precedent, both for sp^2–sp^2 cross-couplings and also for reactions of acyclic systems, we were delighted to find that twofold Negishi reactions of 3,3-dibromo[3]dendralenes **5** with vinylzinc bromide proceed well using [Pd(dppf)Cl_2] as pre-catalyst to form the first unsymmetrical TVEs **6** (Table 2).

3,3-Dibromo[3]dendralenes comprising the same (**5a-g**) or different (**5h-l**) alkenyl substituents performed equally well, to generate the first examples of TVEs possessing two or three different alkenyl groups about the central C=C bond. TVEs bearing carbocyclic aromatic substituents with different electronic characteristics (**6j-l**) and the first TVEs carrying heterocyclic aromatic substituents (**6f-i**) are included in this selection.

Twofold cross-couplings of 3,3-dibromo[3]dendralenes **5** are by no means limited to the introduction of a pair of unsubstituted vinyl groups: in fact, alkenyl groups bearing substituents at any position are tolerated. The syntheses of eighteen of these more highly substituted TVEs are summarized in Table 3. Double Negishi couplings of 3,3-dibromo[3]dendralene **5a** with 2-propenyl-, (*E*)-styrenyl- and (2-methylprop-1-en-1-yl)zinc bromides furnished six novel tetra- and hexa-substituted TVEs **6n-s**. Cross-couplings other than Negishi reactions are also successful, as demonstrated by the products of double Suzuki-Miyaura[17] and Mizoroki-Heck[18] processes, **6t-v** (3 examples)

and **6w-ae** (9 examples), respectively. These results establish the wide scope of the 3,3-dibromo[3]dendralene cross-coupling approach to TVE synthesis and its broad tolerance of substitution upon the incoming alkenyl-groups.

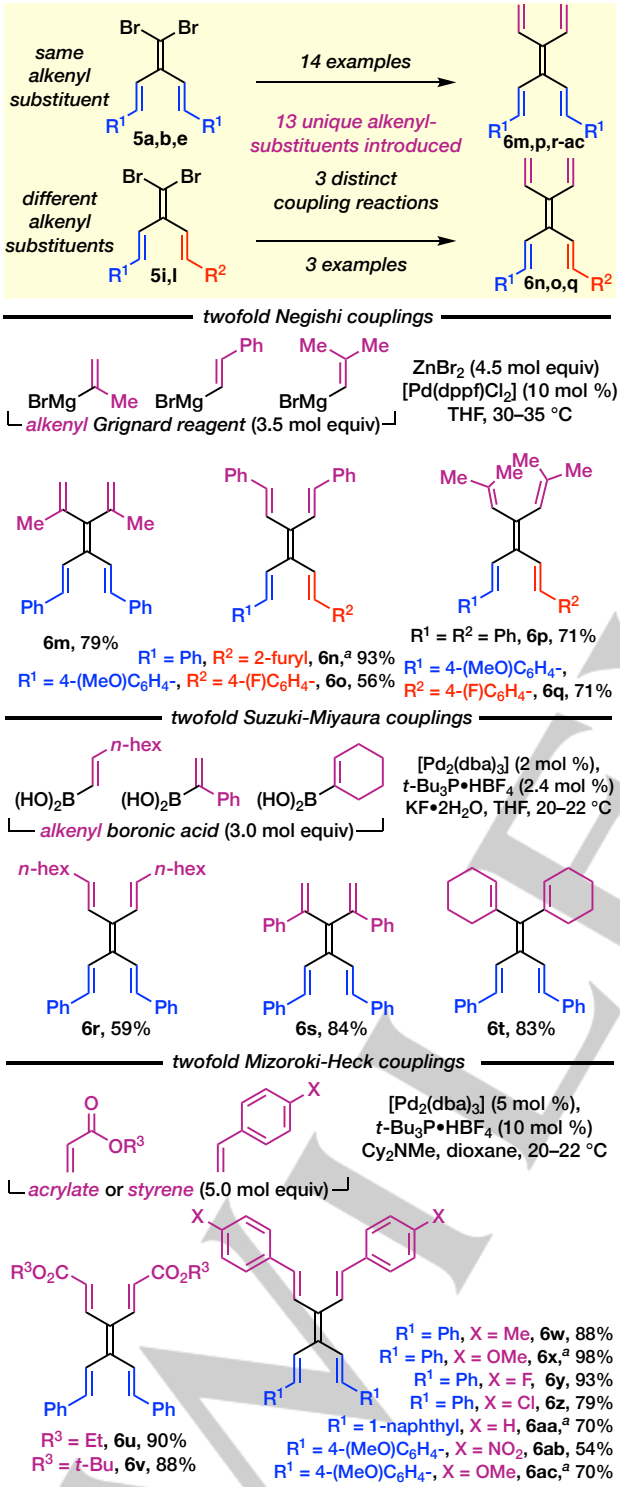
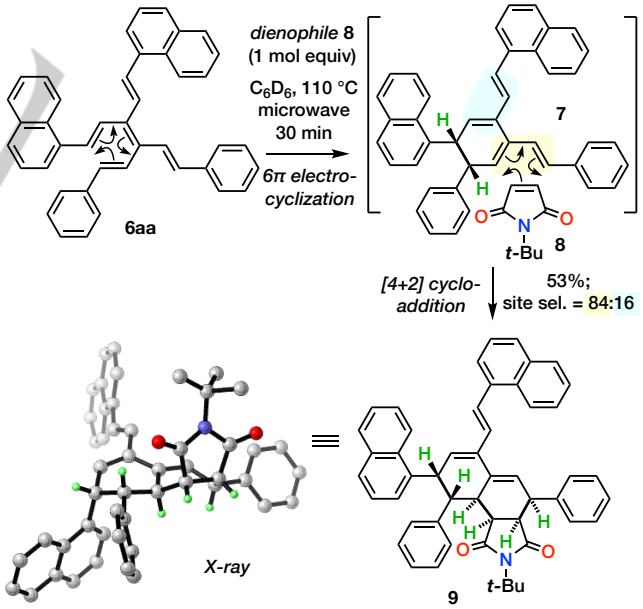


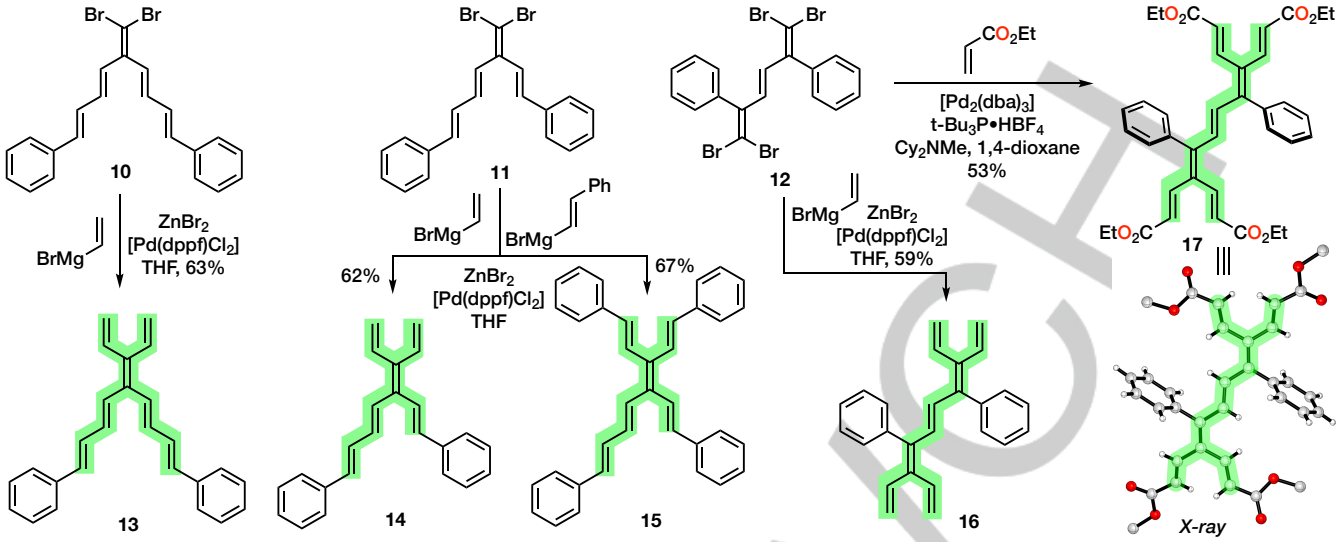
Table 3. Twofold Negishi, Suzuki-Miyaura or Mizoroki-Heck reactions grant access to unsymmetrical, multi-substituted tetravinylethylenes. [a]X-ray crystal structures of these four TVEs[22] are in the SI.

Following the trend previously seen,[4,5] the 25 new TVEs depicted in Tables 2 and 3 are bench-stable substances. No special equipment or methods are required when manipulating these compounds: they survive storage neat at ambient temperature for several weeks. The lack of susceptibility of this new family of π-bond rich systems towards uncatalyzed Diels-Alder dimerization and autoxidation (typical of related cross-conjugated[15] and through-conjugated[19] polyenic systems) bodes well for future applications.

Access to unsymmetrically-substituted TVEs promotes new opportunities in rapid structure complexity generation, and an interesting question of diene site selection in [4+2]cycloadditions of polyenes (Scheme 2). Heating diphenyl-di-(1-naphthyl)-TVE **6aa** in benzene brings about a disrotatory electrocyclization to generate cyclic [4]dendralene[14] **7**, with a *cis*-disposition between the two cyclohexadiene substituents. When performed in the presence of dienophile *N-tert*-butylmaleimide **8**, a subsequent *endo*-mode cycloaddition occurs, with approach to the less sterically encumbered π-diastereoface of [4]dendralene **7**. The two non-equivalent semi-cyclic dienes of [4]dendralene **7** (highlighted in different colors in Scheme 2) are expected to be more reactive than the cyclohexadiene site,[5] and the phenyl-substituted diene is preferred over the 1-naphthyl-substituted site. Overall, this operationally trivial domino sequence generates densely-functionalized decalin **9**, with three new C–C bonds, six contiguous stereocenters, and a cyclic [3]dendralene subunit that invites additional synthetic manipulation.[20]



Scheme 2. Stereoselective domino [6π]electrocyclization/[4+2]cycloaddition of TVE **6ad** proceeds with diene site selectivity to generate multicyclic product **9**. H atoms not attached to stereocenters are omitted from the X-ray crystal structure[22,23] for clarity.



Scheme 3. First preparation of higher order acyclic C=C-based *π*-frameworks related to TVE. The new *π*-systems are highlighted in green. Ethyl groups are truncated in the X-ray crystal structure[22,23] for clarity.

The robust nature of the new pentaene-based TVE compounds, combined with their ease of synthesis, prompted the question of whether larger structures with unprecedented acyclic *π*-frameworks were within reach. The successful extension of these methods to the syntheses of hexaenes **14** and **15**, and heptaenes **13**, **16** and **17** are depicted in Scheme 3. Dibromo-tetraene **10**, dibromo-pentaene **11** and tetrabromo-triene **12**, prepared through Lautens-modified Ramirez dibromo-olefination reactions of commercially available ketonic precursors (see SI), underwent twofold or fourfold Negishi or Mizoroki-Heck couplings to furnish the bench-stable polyenic products. The UV absorption spectrum of heptaene **17** exhibits features attributable to the longest through-conjugated subunit (see SI). The solid state molecular structure of tetra-ester **17**, obtained from single crystal X-ray analysis, is consistent with this observation, revealing an essentially in-plane 2,4,6,8,10-dodecapentaenoate unit (Scheme 3). Acyclic, hybrid cross-conjugated/through-conjugated C=C structures are very poorly represented in the literature.[21] The structures depicted in Scheme 3 represent the first examples of substances of this type.

In summary, we have described the first general synthetic approach to TVEs and related through/cross-conjugated acyclic C=C-based systems. This work reports 34 new TVEs and related structures, including the first examples exhibiting unsymmetrical substitution patterns, extended through-conjugation and/or cross-conjugation. The synthetic approach is robust, involving twofold Negishi, Suzuki-Miyaura or Mizoroki-Heck couplings of acyclic 3,3-dibromo[3]dendralenes. The new structures are bench stable compounds that undergo operationally simple, selective, complexity-generating domino sequences. The acyclic C=C-bond-rich structures described herein are representatives of a sizeable region of structural space that was previously inaccessible but is now available for exploration and investigation. Applications in target synthesis and in conducting materials will follow.

Acknowledgements

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Keywords: hydrocarbons • polyenes • cross-coupling • electrocyclic reactions • cycloaddition

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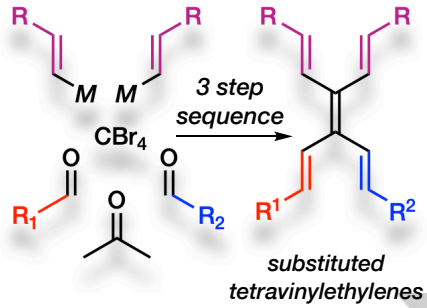
COMMUNICATION

Master key for TVE. The first general synthesis of tetravinylethylenes (TVEs) involves the preparation and cross-coupling of dibromo-[3]dendralenes. Their value in controlled, rapid structural complexity generation is demonstrated. The first higher order acyclic oligo-alkenic through-conjugated/cross-conjugated hybrid compounds are also reported.



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